PSEUDOPOLYMORPHIC FORMS OF A HIV PROTEASE INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of pending U.S. application Ser. No. 10/514,352, filed Nov. 12, 2004, now U.S. Pat. No. 7,700,645 which in turn is a national stage of PCT Application No. PCT/EP2003/50176, filed May 16, 2003, which application claims priority from European Patent Application No. 02076929.5, filed May 16, 2002, the entire disclosures of which are hereby incorporated in their entirely.

TECHNICAL FIELD

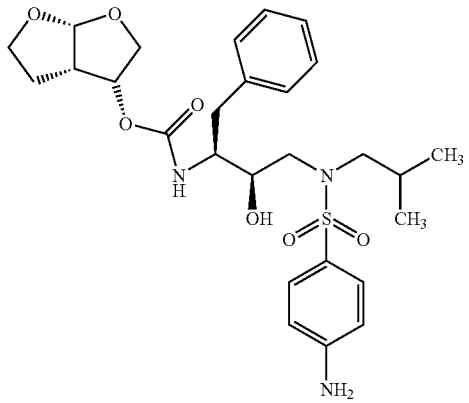
This invention relates to novel pseudopolymorphic forms of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropylcarbamate, a method for their preparation as well as their use as a medicament.

BACKGROUND OF THE INVENTION

Virus-encoded proteases, which are essential for viral replication, are required for the processing of viral protein precursors. Interference with the processing of protein precursors inhibits the formation of infectious virions. Accordingly, inhibitors of viral proteases may be used to prevent or treat chronic and acute viral infections. (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropylcarbamate has HIV protease inhibitory activity and is particularly well suited for inhibiting HIV-1 and HIV-2 viruses.

The structure of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-hydroxypropylcarbamate, is shown below:

Formula (X)



Compound of formula (X) and processes for its preparation are disclosed in EP 715618, WO 99/67417, U.S. Pat. No. 6,248,775, and in *Bioorganic and Chemistry Letters*, Vol. 8, pp. 687-690, 1998, "Potent HIV protease inhibitors incorporating high-affinity P_2-ligands and (R)-(hydroxyethylamino) sulfonamide isostere", all of which are incorporated herein by reference.

Drugs utilized in the preparation of pharmaceutical formulations for commercial use must meet certain standards,

including GMP (Good Manufacturing Practices) and ICH (International Conference on Harmonization) guidelines. Such standards include technical requirements that encompass a heterogeneous and wide range of physical, chemical and pharmaceutical parameters. It is this variety of parameters to consider, which make pharmaceutical formulations a complex technical discipline.

For instance, and as example, a drug utilized for the preparation of pharmaceutical formulations should meet an acceptable purity. There are established guidelines that define the limits and qualification of impurities in new drug substances produced by chemical synthesis, i.e. actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. Guidelines are instituted for the amount of allowed degradation products of the drug substance, or reaction products of the drug substance with an excipient and/or immediate container/closure system.

Stability is also a parameter considered in creating pharmaceutical formulations. A good stability will ensure that the desired chemical integrity of drug substances is maintained during the shelf-life of the pharmaceutical formulation, which is the time frame over which a product can be relied upon to retain its quality characteristics when stored under expected or directed storage conditions. During this period the drug may be administered with little or no risk, as the presence of potentially dangerous degradation products does not pose prejudicial consequences to the health of the receiver, nor the lower content of the active ingredient could cause under-medication.

Different factors, such as light radiation, temperature, oxygen, humidity, pH sensitivity in solutions, may influence stability and may determine shelf-life and storage conditions.

Bioavailability is also a parameter to consider in drug delivery design of pharmaceutically acceptable formulations. Bioavailability is concerned with the quantity and rate at which the intact form of a particular drug appears in the systemic circulation following administration of the drug. The bioavailability exhibited by a drug is thus of relevance in determining whether a therapeutically effective concentration is achieved at the site(s) of action of the drug.

Physico-chemical factors and the pharmaco-technical formulation can have repercussions in the bioavailability of the drug. As such, several properties of the drug such as dissociation constant, dissolution rate, solubility, polymorphic form, particle size, are to be considered when improving the bioavailability.

It is also relevant to establish that the selected pharmaceutical formulation is capable of manufacture, more suitably, of large-scale manufacture.

In view of the various and many technical requirements, and its influencing parameters, it is not obvious to foresee which pharmaceutical formulations will be acceptable. As such, it was unexpectedly found that certain modifications of the solid state of compound of formula (X) positively influenced its applicability in pharmaceutical formulations.

SUMMARY OF THE INVENTION

Present invention concerns pseudopolymorphic forms of compound of formula (X) for the preparation of pharmaceutical formulations. Such pseudopolymorphic forms contribute to pharmaceutical formulations in improved stability and bioavailability. They can be manufactured in sufficient high purity to be acceptable for pharmaceutical use, more particularly in the manufacture of a medicament for inhibiting HIV protease activity in mammals.